REMARKS

The Office Action sent August 7, 2009 has been received and reviewed. All claims stand rejected. The application is to be amended as previously set forth. All amendments are made without prejudice or disclaimer. Support for the amendments and new claims may be found throughout the as-filed Specification and the claims as previously presented. Accordingly, applicants submit that no new matter has been added. Reconsideration is respectfully requested.

Applicants' European counterpart application granted as European Patent No. 1 585 497

Applicants wish to inform the Office that the instant application's European counterpart application was granted as European Patent No. 1,585,497 on March 26, 2008. Applicants believe that the instant application's importance in industry and to the treatment of non-human mammals is illustrated at least in part by a currently pending Opposition against European Patent No. 1,585,497 in the European Patent Office. Enclosed herewith are materials from the currently pending opposition for European Patent No. 1,585,497. *See,* Supplemental Information Disclosure Statement. Applicants believe that the materials submitted herewith, in addition to the amendments and remarks presented herein, more than sufficiently demonstrate the patentability of the instant application and the claims as currently presented.

35 U.S.C. § 103

1. Claims 1-3, 7, and 10 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Farnsworth et al. (Canadian J. of Comp. Med., July 1975, (39): 340-348; hereinafter 'Farnsworth') in view of Lohuis et al. (J. Dairy Sci., 1989 (72): 75-98; hereinafter 'Lohuis'). Claims 2-3 have been canceled, thus rendering the rejection of those claims moot. Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, the prior art itself or "the inferences and creative steps that a person of ordinary skill in the art would [have] employ[ed]" at the time of the invention are to have taught or suggested the claim elements. Additionally, there must have been "a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements" in the manner claimed. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742, 167 L.Ed.2d 705, 75 USLW 4289, 82 USPQ2d 1385 (2007). Further, in

determining obviousness, the teachings of the prior are must be considered in its entirety, including those disclosures that teach away from the claims. MPEP §§ 2145 (X)(D), 2141.02. Finally, a greater than expected result or the presence of an unexpected property is evidence of nonobviousness. *See, e.g., Id.* at § 2144.05, emphasis added.

Applicants submit that none of references relied upon by the Examiner, when combined and/or considered as a whole, teaches or suggests a composition as presently claimed, to wit, comprising, both at least 20 mg of prednisolone and an anti-bacterial agent. Indeed, the teachings of Lohuis teach against modifying the references in accordance with the present claims. Furthermore, as has been asserted in previous responses (*e.g.*, Responses submitted May 27, 2009 and April 8, 2008), and as demonstrated herein, the unexpected results obtained by applicants' claimed composition constitute evidence of the non-obviousness of applicants' claimed composition.

The Office alleges that to one of ordinary skill in the art it would have been obvious to discover the workable optimum ranges of prednisolone through routine experimentation. Office Action of August 7, 2009, pages 9-10. The Office additionally alleges that it would have been obvious to try 40 mg prednisolone in the combinatorial treatment taught in Farnsworth since Lohuis demonstrated that the use of 40 mg had an effect upon inflammation. *Id.*

Applicants respectfully disagree and note that to establish obviousness based upon "routine experimentation" or "obvious to try" rationales, the resultant combination and the efficacy thereof must have been reasonably predictable prior to applicants' invention. MPEP § 2145 (X)(B). Furthermore, any support for the predictably of applicants' claimed composition cannot be based upon applicants' disclosure. *Id.* at § 2145(X)(A).

In view of the unexpected results and properties of applicants' claimed composition, as described herein and in previous responses (*e.g.*, increased anti-inflammatory efficacy while not increasing immunosuppressive side effects and a similar leukocyte count upon administration to the non-human mammal when administered intramammarily, as compared to the non-human mammal to whom the pharmaceutical composition has not been thus administered), it would not have been obvious for a person of ordinary skill in the art to combine and modify Farnsworth and Lohuis as presently claimed.

The present claims are further not obvious as the prior art, when considered as whole,

teaches against a combination with Farnsworth and Lohuis in accordance with the present claims. For example, Lohuis suggests that using increased dosages of intramammarily administrated prednisolone to treat mastitis infections would not have an increased or an enhanced anti-inflammatory effect. *See, e.g.,* Lohuis, abstract Figure 1A. Indeed, Lohuis states"[a]ll corticosteroid treatments, except intramammary administration of prednisolone 4 h after endotoxin infusion enhanced leukocytosis and diminished local signs of inflammation." *Id.* emphasis added. Clearly, this would have suggested to a person of ordinary skill in the art that increased intramammary dosages of prednisolone would not have resulted in increased anti-inflammatory effects.

Applicants acknowledge that Lohuis does teach that there was an enhanced anti-inflammatory effect using an intramuscular injection of the long acting glucocorticosteroids dexamethasone or flumethasone together with the intramammary administration of prednisolone. *Id.* However, only after the intramammary administration of prednisolone together with the intramuscular injection of the dexamethasone or flumethasone was there any enhanced anti-inflammatory effect. *Id.* Based upon this teaching, a person of ordinary skill in the art would have reasonably concluded and expected that the intramammary administration of prednisolone alone was not a contributing factor or was otherwise not a significant factor in enhancing anti-inflammatory effects.

In view of the fact that Louis expressly teaches the absence of any enhanced anti-inflammatory effects for prednisolone when administered intramammarily by itself, a person of ordinary skill in the art would not have reasonably predicted an enhanced anti-inflammatory effect resulting from an intramammary administration of increased dosages of prednisolone without the intramuscular injection of the dexamethasone or flumethasone (*see, e.g.,* claim 11, wherein the active agents consist of cephapirin and prednisolone).

In accordance with Lohuis, a person of ordinary skill in the art would not have been motivated to increase and/or modified the dosage of prednisolone as taught in Farnsworth in accordance with the claimed composition. Furthermore, because Lohuis teaches that the intramammary administration of prednisolone was not a contributing or not a significant factor in enhancing anti-inflammatory effects, the person of ordinary skill in the art would not have reasonably expected or predicted an increase in anti-inflammatory effects, in addition to the lack

of significant increase in immunosuppressive side effects as presently claimed.

The Office repeatedly alleges that since the claims were allegedly rendered obvious over the combination of Farnsworth and Lohuis (but see above), one cannot show non-obviousness by attacking references individually, where the rejections are based on combinations of references. *See,* Office Action at page 4-6 citing *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). Applicants respectfully note that "teaching away" may be demonstrated by a reference's teaching in combination with the prior art as a whole.[1] *See, e.g.,* MPEP 2145 (X)(D) and *In re Merck & Co.* 231 USPQ at 380.

Based upon MPEP 2145 (X)(D) and the supporting case law, Lohuis should not be read in isolation, but rather Lohuis should be considered for what it teaches in combination with prior art as whole, such as Farnsworth. As acknowledged by the Office, Farnsworth does not teach a composition comprising at least 20 mg of prednisolone per unit dose (Office Action at 9), nor does Farnsworth teach or suggest that increasing the dosages prednisolone would have resulted in an increase in anti-inflammatory effects, in addition to the lack of significant increase in immunosuppressive side effects as presently claimed. Farnsworth, when combined with Lohuis's teachings (*e.g.*, the absence of any enhanced anti-inflammatory effects for prednisolone when administered intramammarily by itself), clearly demonstrates that a person of ordinary skill in the art would not have been motivated to increase the dosages of prednisolone in Farnsworth where the active ingredients are prednisolone and a cephalosporsin (*see, e.g.,* claim 11). Indeed, as previously discussed, Lohuis teaches that such a composition without an intramuscular injection of the dexamethasone or flumethasone did not have an enhanced anti-inflammatory effect.

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[1] MPEP § 2145 (V) does state that one cannot show non-obviousness by attacking the references individually. However, MPEP § 2145 (V) does not preclude demonstrating non-obviousness via prior art disclosures that teach away from a claimed method or device. Indeed, such demonstration is not "attacking" since the prior art is not being attacked or the content disputed. This becomes more clear when considering MPEP § 2145 (X) (D) and *In re Merck & Co.,* the case law from § 2145 (V). MPEP § 2145 (X) (D) expressly states that "the prior art must be considered in its entirety, including disclosures that teach away from the claims." MPEP 2141.02 (VI)(D). This is further supported by *Merck & Co.,* wherein the Court of Appeals for the Federal Circuit indicated that a reference must not be read in isolation, but rather what it teaches in combination with the prior art as whole. *See, Merck,* 231 USPQ at 380.

In view of fact that Lohuis' teaches against a combination with Farnsworth and the lack of reasonable predictability, applicants submit that the claims are not obvious as it would not have been "obvious to try," nor would it have been a matter of "routine experimentation" for a person of ordinary skill in the art to have combined or modified the prior art references in accordance with the presently claimed composition. *See, e.g.,* MPEP §§ 2143.01 (III), 2144.05 (II).

Unexpected Results of the Claimed Dosages demonstrate non-obviousness

Even if a *prima facie* case of obviousness had been established in view of Farnsworth and Lohuis (which, applicants dispute herein), claims 1-3, 7, and 10 are not obvious as the claimed composition provides significant and unexpected results, to wit, increased anti-inflammatory efficacy while unexpectedly not increasing immunosuppressive side effects as compared to compositions comprising less prednisolone. *See, e.g.,* as-filed Specification at Examples 4-5.

In response to the applicants' previous response, the Office alleges that applicants' demonstration of unexpected results is not persuasive and is moot as applicants were "arguing features that are not present in the claims." Office Action at 2-3. The Office further alleges that "although the claims are interpreted in light of the Specification, limitations from the specification are not read in into the claims." *Id.*, citing *In re Van Geuns,* 988 F.2d 1181, 26 USPQ2d 1057.

Applicants respectfully submit that the Office is incorrectly applying and defining "limitations" and *In re Van Geuns.* Indeed, the MPEP does state that limitations from the specification should not be read into the claims. MPEP § 2145 (VI). However, § 2145 (VI) is inapposite to the current issue, as § 2145 (VI) is directed to "limitations" and does not pertain to evidence of non-obviousness. MPEP § 716.02 explicitly states that advantages, criticalities, and inherent properties need not even be disclosed in the specification to be considered as evidence of nonobviousness. *Cf.* §2145 (VI) and § 716.02 (f). Additionally, numerous courts have found that evidence of nonobviousness, including unexpected results, need not be specified in one or more claims. *See, e.g., In re Sullivan* 498 F. 3d 1345, 84 USPQ 2D 1034 (Fed. Cir. 2007); *In re Soni,* 54 F3d 746, 747, 34 USPQ2d 1684, 1685 and 1687 (Fed. Cir. 1995); *In re Margolis,* 785 F2d 1029, 228 USPQ 940 (Fed. Cir. 1986); *In re Geisler,* 116 F3d 1465, 43 USPQ 2d 1362 (Fed.

Cir. 1997).

In the previous responses, applicants have demonstrated and asserted that the claimed composition provides increased anti-inflammatory efficacy while unexpectedly not increasing immunosuppressive side effects as compared to compositions comprising less prednisolone. *See, e.g.,* Response submitted May 27, 2009, pages 6-9. The previous responses further show where the teachings of the prior art, to wit Lohuis, demonstrated that the claimed composition and the properties and results, as claimed were unexpected. *See, e.g., id.* Indeed, Lohuis does not teach or suggest that higher dosages of prednisolone with an antibacterial compound can provide increased anti-inflammatory efficacy while not increasing immunosuppressive side effects. *See, e.g., id.* at 7. Furthermore, the different experimental results obtained by applicants using both prednisolone and an antibacterial compound, suggests that using higher prednisolone dosages with an anti-bacterial compound does not have similar effects as the administration of prednisolone as taught in Lohuis. *Id.*

As noted in the previous response, the as-filed Specification outlines exemplary manners in which the efficacy of the presently claimed composition is unexpectedly improved. In Example 4, the Specification describes experimental results stating:

> "total leukocyte counts in blood is lower in cows treated with [the antibacterial agent] cephapirin and prednisolone (group 3) than in cows treated with cephapirin alone, but not different from total leukocyte counts in blood from not treated cows." *See, e.g.,* as-filed application, page 12, lines 26-30, emphasis added.

As described in the foregoing passage, administration with both cephapirin and prednisolone was not different from those animals that were untreated or did not receive the composition. Based on the references relied upon by the Examiner, one of ordinary skill in the art would not have expected this. For example, Lohuis' teaches contrasting results, to wit, a substantial increase in leukocyte counts of prednisolone as compared to non-treated animals. *See, e.g.,* Lohuis, Figure 3, and Final Office Action, page 3. Applicants respectfully note that the language of claims 1 and 7 are consistent with these unexpected results. More particularly, the language of claims 1 and 11 specifically outline these unexpected results.

Example 4 of the as-filed Specification provides another way in which the efficacy of applicants' claimed composition is unexpectedly improved. Example 4 states, in part,

> "[a]t 24 h after endotoxin infusion the chemotaxis of blood PMNs was higher in group 3 than in group 1 or 2. (Table 2 and FIG. 4). 20 mg prednisolone seems to increase the ability of PMN to migrate into the udder since chemotaxis of blood PMNs increases after intramammary infusion of cephaprin and 20 mg of prednisolone."
> As-filed Specification at 13, lines 21-26.

Thus, applicants' claimed composition provides significantly improved chemotaxis of PMNs (polymorphonuclear leukocytes), and as indicated above by the Specification, increases the ability of the PMNs to migrate into the udder. *Id.* This significant improvement is further illustrated in Figure 4. Applicants respectfully note that the language of claim 10 is consistent with these unexpected results.

In responding to applicants' previous remarks with regard to Lohuis, the Office contends that these arguments are not persuasive as one cannot show non-obviousness by attacking references individually. Office Action at 4. However, as previously set forth herein, applicants are not "attacking" or "disputing" the content of Lohius. *See, supra,* page 8. Rather, applicants are referencing the teachings of Lohuis as they are representative of the expectations and understanding in the prior art with regard to increased dosages of prednisolone in the intramammary treatment of mastitis. Accordingly, the teachings of Lohuis are relevant and should be considered when determining whether the claims are obvious and unexpected.

The Office further alleges that the unexpected results are not commensurate with the claimed composition as previously claimed, as allegedly all of the unexpected results provided by applicants demonstrate the sole use of 20 mg prednisolone. Office Action at 3. While applicants do not agree with the Office, in order to expedite prosecution, claims 10 and 11 are presented and are directed to a composition including 20 mg prednisolone (*see,* claims 10-12).

The Office additionally alleges that the applicants failed to demonstrate any comparative data to show that the prior art's teachings of 10 mg of prednisolone would not necessarily result in a lowering of PMN total leukocyte counts and that the applicants must show the criticality of the claimed dosages. *Id.*

Applicants respectfully disagree with the Office and note that while the MPEP provides that comparative data may be used to show non-obviousness, comparative data and criticality are not required to demonstrate unexpected results. MPEP §§ 716.02, 2144.05. Rather, in

determining obviousness and any unexpected results, the totality of the record must be considered. *Id.* at 716.02(c)(f). For example, "unexpected results for a claimed range as compared with the range disclosed in the prior art had been shown by a demonstration of 'a marked improvement, over the results achieved under other ratios, as to be classified as a difference in kind, rather than one of degree.'" *Id.* citing *In re Wagner*, 371 F.2d 877, 884, 152 USPQ 552, 560 (C.C.P.A. 1967).

Applicants submit that when the totality of the record is considered, the unexpected results more than sufficiently demonstrate the non-obviousness of the claimed composition. For example, in the instant case, the unexpected results and properties of the claimed compositions would have been characterized as differences in kind rather than degree, *e.g.,* increased anti-inflammatory efficacy while not increasing immunosuppressive side effects, and an increased chemotaxis of blood leukocytes (claim 10). As previously demonstrated, the teaching of Lohuis indicates that such results were unexpected prior to applicants' invention.

Applicants respectfully submit that claims 1, 7, and 10 are not obvious over Farnsworth and Lohuis, at least in view of the fact that Lohuis teaches against increasing the dosages of prednisolone without adding additional active agents, to wit, dexamethasone or flumethasone (*see, e.g.,* claim 11), thus a person of ordinary skill in the art would not have been motivated to modify Farnsworth and Lohuis to composition having increased prednisolone dosages without dexamethasone or flumethasone. Claims 1-3, 7, and 10 are additionally not obvious as the totality of the evidence and knowledge in the art prior to applicants' invention indicates that the properties and results of the claimed compositions would have been unexpected.

Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. § 103 rejections of claims 1-3, 7, and 10.

2. Claims 4-6 and 11 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Farnsworth in view of Lohuis and in further view of Hornish et al. (Current Topics in Med. Chem. July 2002 (2):717-731; hereinafter 'Hornish'). Applicants respectfully traverse the rejection as follows.

Claims 4-6 directly or indirectly depend from claim 1, and therefore, are patentable over

the references relied upon by the Examiner for at least the same reasons as claim 1.

Applicants additionally submit that claim 11 is not obvious over Farnsworth in view of Lohuis and in further view of Hornish. Claim 11 recites, in part,

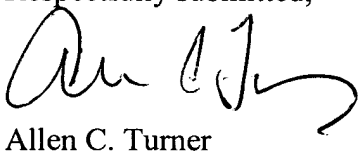
> "the pharmaceutical composition comprises active agents and inactive agent, wherein the active agents ~~consists~~ consist of cephapirin and 20 mg prednisolone; and the inactive agent comprises a pharmaceutically acceptable carrier"

As previously set forth herein, the prior art when considered as whole teaches against combining Farnsworth and Lohuis in accordance with the composition of claim 11. Indeed, Lohuis when combined with Farnsworth teaches that absent dexamethasone or flumethasone, prednisolone has no enhanced ant-inflammatory effects. Accordingly, a person of ordinary skill the art, based upon the teachings of Farnsworth and Lohuis, would not have expected any enhanced or increased effects by increasing the dosages in a composition wherein prednisolone and an anti-bacterial agent were active ingredients. As such, it would not have been considered "obvious to try," or merely "routine experimentation" to make the composition as presently recited in claim 11.

In view of remarks and amendments herein, applicants submit that claim 11 is not obvious over Farnsworth in view of Lohuis and in further view of Hornish. Reconsideration and withdrawal of the rejections are respectfully requested.

In light of the foregoing amendments and remarks, the application should be in condition for allowance. If questions remain after consideration of the foregoing, or if the Office should determine that there are additional issues which might be resolved by a telephone conference, the Office is kindly requested to contact applicants' attorney at the address or telephone number given herein.

Respectfully submitted,



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